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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,172	11/16/2001	Avi J. Ashkenazi	P2730P1C50	3269

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HELLER EHRMAN WHITE & MCAULIFFE LLP  
275 MIDDLEFIELD ROAD  
MENLO PARK, CO 94025-3506

EXAMINER

KAUFMAN, CLAIRE M

ART UNIT PAPER NUMBER

1646

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No.

09/991,172

Applicant(s)

ASHKENAZI ET AL.

Examiner

Claire M. Kaufman

Art Unit

1646

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 16 November 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 119-138 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 119-128 and 130-138 is/are rejected.
- 7) ☒ Claim(s) 129 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 November 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>5/28/02</u> . | 6) <input checked="" type="checkbox"/> Other: <u>sequence comparison</u> .              |

### **DETAILED ACTION**

The preliminary amendment filed 11/16/01 has been entered.

#### **Claim Rejections - 35 USC § 112**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 132, 133 and dependent claims 134-138 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 132 and 133 are indefinite because the metes and bounds of the claims are not clear. For claim 132 it is not clear if hybridization under any condition is permissible, even the most permissive, allowing non-specific hybridization to occur. For claim 133, while the skilled artisan understands the general concept of hybridization under "stringent conditions", what specific conditions are intended by the use of the term "stringent" in the present claims is unknown. What conditions of stringency are used in any particular situation are determined by the specificity of hybridization desired by the practitioner. The instant specification presents examples but not a limiting definition of "stringent conditions" (p. 312, line 23, through p. 313, line 4). In this case, the desired specificity is unknown. "Stringent" carries a meaning of "constricted", implying that not all hybridization conditions are acceptable. If however, there is a structural relatedness (limitation) that is being defined by the conditions, then those conditions or range of conditions must be clear in the claim.

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 119-124, 127, 128 and 132-134 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid of SEQ ID

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NO:51 or which encodes the protein of SEQ ID NO:52 or the protein of SEQ ID NO:52 except lacking its associated signal sequence, does not reasonably provide enablement for other nucleic acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

uw The nucleic acid of SEQ ID NO:5<sup>1</sup>~~2~~ encodes a protein called PRO1282 which is 673 amino acids long, with a putative signal sequence from residue 1-23, transmembrane domain from 579-599, leucine zipper region from 197-269 and EGF-like domain beginning at 430 (p. 414, lines 13-16). The encoded protein tested positive in the Chondrocyte Redifferentiation Assay (#110, p. 530) and the nucleic acid was shown to have a  $\Delta C_t$  slightly greater than 1 for 2/17 colon tumors ( $\Delta C_t = 1.15$  and 1.07) tested and none of the 12 lung tumors tested (p. 554).

w The claims are broad, including nucleic acids encoding only an extracellular domain of SEQ ID NO:5~~1~~ and nucleic acids 80% identical to thereto. There is no functional limitation associated with the nucleic acid or encoded protein in the claims. Aside from the positive outcome in the chondrocyte redifferentiation assay there is no function associated with PRO1282, and its specific role in the redifferentiation is not disclosed.

Blast results submitted by Applicant and other sequence comparison shows that PRO1282 is most structurally related to slit and riken proteins, however, the function of these proteins is unclear. Itoh et al. cloned human homologues of *Drosophila* slit and suggests a possible role for mammalian slit in formation and maintenance of the nervous and endocrine system based on its role in *Drosophila* and its tissue expression in human

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and rat (p. 185, 2 paragraphs beginning the last paragraph of col. 1). It is also noted that *Drosophila slit* is not expressed in neuronal cells, but rat *slit-1* and human *slit-1*, -2 and -3 are (last 2 sentences of last paragraph in col. 1, p. 185). The prior art does not provide sufficient information to allow the skilled artisan to use PRO1282 or the encoding nucleic acid without significant further research.

While the nucleic acid showed slight amplification in 2 tumor cells lines compared to normal tissue, this does not support a diagnostic use of the nucleic acid for detection of cancerous tissue. There are several reasons for this. Elevated copy number in 2/17 colon cancers does not provide the skilled artisan with a reasonable expectation that PRO1218 DNA copy number can serve as a marker for colon cancer since expression was in such a small minority of the tumors tested. Further, Lanza et al. (Cancer, 82:49, 1998) showed that out of 191 colon carcinomas tested, 144 (75.4%) had aneuploid DNA (p. 51, col. 2, third full paragraph). That means an increased copy number for PRO1218 in the colon tumors tested was less like due to an increase unique to PRO1282 DNA, but rather due to a more general phenomenon of aneuploidy of the DNA in those colon cancer cells. Another study of aneuploidy in colon cancers showed that in some individuals with colon cancer, aneuploidy was also found in morphologically normal colon tissue (Fleischhacker et al., Modern Path., 8:360, 1995; *e.g.*, p. 360, col. 2). Because aneuploid DNA can be found in normal tissue, detection of increased DNA copy number does not necessary mean those cells containing the DNA are cancerous. Further, the  $\Delta Ct$ 's of the PRO1282 DNA were extremely low, and the specification says on p. 548, lines 35-36, that "...the CT value of normal human DNA subtracted from test DNA was +/-1 Ct." In light of this, it is questionable whether a CT value of 1.07 or even 1.15 can be considered significant. Therefore in this instance, copy number does not support a basis for how to use the claimed nucleic acid.

While the PRO1282 protein (probably the mature form) lead to redifferentiation in the chondrocyte assay, the specification provides no information on what domains or characteristics of the protein were responsible for its effect on chondrocytes. It is unpredictable if the extracellular domain alone has the necessary function. Indeed, one skilled in the art would expect that signal transduction would be necessary for

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chondrocyte redifferentiation, and a soluble polypeptide cannot transduce a signal unless it is a soluble ligand able to bind to and activate a receptor. The structural elements identified by Applicants for PRO1282 makes it unlikely that it is normally a soluble ligand. Based on PRO1282's homology to slit discussed above, one could not have predicted a reasonable expectation of successful in cause chondrocyte redifferentiation. While the PRO1282 protein of SEQ ID NO:52 (with or without the signal sequence) was functional in this assay, it is, at the least, unpredictable what changes could be made to SEQ ID NO:52 while retaining its redifferentiation ability.

For these reasons which include breadth of the claims, lack of information on the relationship of structure to function of PRO1282, paucity of information in the prior art, limited working example, and lack of guidance for use provided in the specification, it would require undue experimentation to use the claimed nucleic acid commensurate in scope with the claims.

Claims 119-124, 127, 128 and 132-134 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a nucleic acid having at least 80%, 85%, 90%, 95% or 99% sequence identity to a nucleic acid encoding a polypeptide with a particular disclosed sequence or drawn to a nucleic acid that hybridizes to SEQ ID NO:51. The claims do not require that the nucleic acid or encoded polypeptide possess any particular biological activity, nor any particular conserved structure or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of nucleic acids that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any

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combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Which nucleic acids of the genus comprising the required sequence are part of the invention has not been set forth.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF’s were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated nucleic acids comprising SEQ ID NO:51 or which encode the polypeptide of SEQ ID NO:52, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

***Priority***

Priority application 09/380,137 and earlier filed priority applications do *not* meet the requirements of 35 U.S.C. § 112, first paragraph. Because there was no function associated with PRO1282 and the skilled artisan would not have known how to use it, the prior application also does not meet those requirements and, therefore, is unavailable under 35 U.S.C. § 120. Note that even if priority were granted to the earliest filed priority application 60/097,979, the art rejection below would remain under 35 UCS 102(e).

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 119-128 and 130-138 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,225,085.

US 6,225,085 teaches a LRSG (leucine-rich surface glycoprotein) of SEQ ID NO:2 which is identical to SEQ ID NO:52 of the instant application. The coding region of the LRSG nucleic acid is identical to that of SEQ ID NO:51 (see attached SEQUENCE COMPARISON). Also disclosed is the encoded protein without or optionally with its signal sequence or with only an extracellular domain (col. 7, lines 1-27), as well as the nucleic acid in a vector and expressed in, for example, *E. coli* (e.g., col. 28, lines 28-45).



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***Claim Objections***

Claim 129 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571)272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 8:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (571)272-0871.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 872-9306. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Claire M. Kaufman, Ph.D.



Patent Examiner, Art Unit 1646

March 17, 2004

SEQUENCE COMPARISON OF SEQ ID NO:52 WITH US 6,225,085

```
; Sequence 2, Application US/09063950C
; Patent No. 6225085
; GENERAL INFORMATION:
; APPLICANT: Holtzman, Douglas A.
; TITLE OF INVENTION: NOVEL LRSG PROTEIN AND NUCLEIC ACID MOLECULES AND USES
; TITLE OF INVENTION: THEREFOR
; CURRENT APPLICATION NUMBER: US/09/063,950C
; CURRENT FILING DATE: 1998-04-21
; SEQ ID NO 2
; LENGTH: 673
; TYPE: PRT
; ORGANISM: Homo sapiens
US-09-063-950-2
```

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Query Match          100.0%; Score 3520; DB 3; Length 673;
Best Local Similarity 100.0%; Pred. No. 5.8e-249;
Matches 673; Conservative 0; Mismatches 0; Indels 0; Gaps 0;
```

```
Qy      1 MCSRVPLLLPLLLLLLALGPGVQGCPSGCQCSQPQTVFCTARQGTTPVRDVPDPDTVGLYVF 60
      |||
Db      1 MCSRVPLLLPLLLLLLALGPGVQGCPSGCQCSQPQTVFCTARQGTTPVRDVPDPDTVGLYVF 60

Qy     61 ENGITMLDAGSFAGLPGLQLLDLSQNQIASLPSGVFQPLANLSNLDLTANRLHEITNETF 120
      |||
Db     61 ENGITMLDAGSFAGLPGLQLLDLSQNQIASLPSGVFQPLANLSNLDLTANRLHEITNETF 120

Qy    121 RGLRRRLERLYLGKNRIRHIQPGAFDTLDRLLELKLQDNELRALPPLRLPRLLLLDLSHNS 180
      |||
Db    121 RGLRRRLERLYLGKNRIRHIQPGAFDTLDRLLELKLQDNELRALPPLRLPRLLLLDLSHNS 180

Qy    181 LLALEPGILDTANVEALRLAGLGLQQLDEGLFSRLRNLDLDVSDNQLERVPPVIRGLRG 240
      |||
Db    181 LLALEPGILDTANVEALRLAGLGLQQLDEGLFSRLRNLDLDVSDNQLERVPPVIRGLRG 240

Qy    241 LTRLRLAGNTRIAQLRPEDIAGLAALQELDVSNLSLQALPGDLSGLFPRLRLIAAARNPF 300
      |||
Db    241 LTRLRLAGNTRIAQLRPEDIAGLAALQELDVSNLSLQALPGDLSGLFPRLRLIAAARNPF 300

Qy    301 NVCPLSWFGPWVRESHVTLASPEETRCHFPKKNAGRLLLELDYADFGCPATTTTATVPT 360
      |||
Db    301 NVCPLSWFGPWVRESHVTLASPEETRCHFPKKNAGRLLLELDYADFGCPATTTTATVPT 360

Qy    361 TRPVVREPTALSSSLAPTWLSPTAPATEAPSPPSTAPPTVGPVPQPDCCPPSTCLNGGTC 420
      |||
Db    361 TRPVVREPTALSSSLAPTWLSPTAPATEAPSPPSTAPPTVGPVPQPDCCPPSTCLNGGTC 420

Qy    421 HLGTRHHLACLCEGFTGLYCESQMGQTRPSPTPVTPRPPRSLTLGIEPVSPTSIRVGL 480
      |||
Db    421 HLGTRHHLACLCEGFTGLYCESQMGQTRPSPTPVTPRPPRSLTLGIEPVSPTSIRVGL 480

Qy    481 QRYLQGSSVQLRSLRLTYRNLSGPDKRLVTLRLPASLAEYTVTQLRPNATYSVCMPLGP 540
      |||
Db    481 QRYLQGSSVQLRSLRLTYRNLSGPDKRLVTLRLPASLAEYTVTQLRPNATYSVCMPLGP 540
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Qy 541 GRVPEGEEACGEAHTPPAVHSNHAPVTQAREGNLPILLIAPALAAVLLAALAAVGAAYCVR 600  
|||||  
Db 541 GRVPEGEEACGEAHTPPAVHSNHAPVTQAREGNLPILLIAPALAAVLLAALAAVGAAYCVR 600

Qy 601 RGRAMAAAAQDKGQVGPGAGPLELEGVKVPLEPGPKATEGGGEALPSGSECEVPLMGFPG 660  
|||||  
Db 601 RGRAMAAAAQDKGQVGPGAGPLELEGVKVPLEPGPKATEGGGEALPSGSECEVPLMGFPG 660

Qy 661 PGLQSPLHAKPYI 673  
|||||  
Db 661 PGLQSPLHAKPYI 673

**SEQUENCE COMPARISON OF SEQ ID NO:51 WITH US 6,225,085**

```
; Sequence 1, Application US/09063950C
; Patent No. 6225085
; GENERAL INFORMATION:
; APPLICANT: Holtzman, Douglas A.
; TITLE OF INVENTION: NOVEL LRSG PROTEIN AND NUCLEIC ACID MOLECULES AND USES
; TITLE OF INVENTION: THEREFOR
; FILE REFERENCE: MEI-019
; CURRENT APPLICATION NUMBER: US/09/063,950C
; CURRENT FILING DATE: 1998-04-21
; NUMBER OF SEQ ID NOS: 9
; SOFTWARE: PatentIn Ver. 2.0
; SEQ ID NO 1
; LENGTH: 2852
; TYPE: DNA
; ORGANISM: Homo sapiens
; FEATURE:
; NAME/KEY: CDS
; LOCATION: (160)..(2178)
US-09-063-950-1
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Query Match          99.5%; Score 2754.4; DB 3; Length 2852;
Best Local Similarity 99.9%; Pred. No. 0;
Matches 2767; Conservative 0; Mismatches 1; Indels 2; Gaps 1;
```

```
Qy=NO:51      1 ACTCGAACGCAGTTGCTTCGGGACCCAGGACCCCTCGGGCCCCGACCCGCCAGGAAAGAC 60
               |||
Db            41 ACTCGAACGCAGTTGCTTCGGGACCCAGGACCCCTCGGGCCCCGACCCGCCAGGAAAGAC 100

Qy            61 TGAGGCCGCGGCCTGCCCCGCGGCTCCCTGCGCCGCCCGCCCTCCCGGGACAGAAGA 120
               |||
Db           101 TGAGGCCGCGGCCTGCCCCGCGGCTCCCTGCGCCGCCCGCCCTCCCGGGACAGAAGA 160

Qy            121 TGTGCTCCAGGGTCCCTCTGCTGCTGCCGCTGCTCCTGCTACTGGCCCTGGGGCCTGGGG 180
               |||
Db           161 TGTGCTCCAGGGTCCCTCTGCTGCTGCCGCTGCTCCTGCTACTGGCCCTGGGGCCTGGGG 220

Qy            181 TGCAGGGCTGCCCATCCGGCTGCCAGTGCCAGCCAGCCACAGACAGTCTTCTGCACTGCCC 240
               |||
Db           221 TGCAGGGCTGCCCATCCGGCTGCCAGTGCCAGCCAGCCACAGACAGTCTTCTGCACTGCCC 280

Qy            241 GCCAGGGGACCACGGTGCCCCGAGACGTGCCACCCGACACGGTGCGGGCTGTACGTCTTTG 300
               |||
Db           281 GCCAGGGGACCACGGTGCCCCGAGACGTGCCACCCGACACGGTGCGGGCTGTACGTCTTTG 340

Qy            301 AGAACGGCATCACCATGCTCGACGCAGGCAGCTTTGCCGGCCTGCCGGGCCTGCAGCTCC 360
               |||
Db           341 AGAACGGCATCACCATGCTCGACGCAGGCAGCTTTGCCGGCCTGCCGGGCCTGCAGCTCC 400

Qy            361 TGGACCTGTCACAGAACCAGATCGCCAGCCTGCCCAGCGGGGTCTTCCAGCCACTCGCCA 420
               |||
Db           401 TGGACCTGTCACAGAACCAGATCGCCAGCCTGCCCAGCGGGGTCTTCCAGCCACTCGCCA 460

Qy            421 ACCTCAGCAACCTGGACCTGACGGCCAACAGGCTGCATGAAATCACCAATGAGACCTTCC 480
               |||
Db           461 ACCTCAGCAACCTGGACCTGACGGCCAACAGGCTGCATGAAATCACCAATGAGACCTTCC 520
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Qy	481	GTGGCCTGCGGCGCCTCGAGCGCCTCTACCTGGGCAAGAACCGCATCCGCCACATCCAGC	540
Db	521	GTGGCCTGCGGCGCCTCGAGCGCCTCTACCTGGGCAAGAACCGCATCCGCCACATCCAGC	580
Qy	541	CTGGTGCCTTCGACACGCTCGACCGCCTCCTGGAGCTCAAGCTGCAGGACAACGAGCTGC	600
Db	581	CTGGTGCCTTCGACACGCTCGACCGCCTCCTGGAGCTCAAGCTGCAGGACAACGAGCTGC	640
Qy	601	GGGCACTGCCCCGCTGCGCCTGCCCCGCCTGCTGCTGCTGGACCTCAGCCACAACAGCC	660
Db	641	GGGCACTGCCCCGCTGCGCCTGCCCCGCCTGCTGCTGCTGGACCTCAGCCACAACAGCC	700
Qy	661	TCCTGGCCCTGGAGCCCCGGCATCCTGGACACTGCCAACGTGGAGGCGCTGCGGCTGGCTG	720
Db	701	TCCTGGCCCTGGAGCCCCGGCATCCTGGACACTGCCAACGTGGAGGCGCTGCGGCTGGCTG	760
Qy	721	GTCTGGGGCTGCAGCAGCTGGACGAGGGGCTCTTCAGCCGCTTGCGCAACCTCCACGACC	780
Db	761	GTCTGGGGCTGCAGCAGCTGGACGAGGGGCTCTTCAGCCGCTTGCGCAACCTCCACGACC	820
Qy	781	TGGATGTGTCCGACAACCAGCTGGAGCGAGTGCCACCTGTGATCCGAGGCCTCCGGGGCC	840
Db	821	TGGATGTGTCCGACAACCAGCTGGAGCGAGTGCCACCTGTGATCCGAGGCCTCCGGGGCC	880
Qy	841	TGACGCGCCTGCGGCTGGCCGGCAACACCCGCATTGCCAGCTGCGGGCCGAGGACCTGG	900
Db	881	TGACGCGCCTGCGGCTGGCCGGCAACACCCGCATTGCCAGCTGCGGGCCGAGGACCTGG	940
Qy	901	CCGGCCTGGCTGCCCTGCAGGAGCTGGATGTGAGCAACCTAAGCCTGCAGGCCCTGCCTG	960
Db	941	CCGGCCTGGCTGCCCTGCAGGAGCTGGATGTGAGCAACCTAAGCCTGCAGGCCCTGCCTG	1000
Qy	961	GCGACCTCTCGGGCCTCTTCCCCCGCCTGCGGCTGCTGGCAGCTGCCCCGAACCCCTTCA	1020
Db	1001	GCGACCTCTCGGGCCTCTTCCCCCGCCTGCGGCTGCTGGCAGCTGCCCCGAACCCCTTCA	1060
Qy	1021	ACTGCGTGTGCCCCCTGAGCTGGTTTGGCCCCCTGGGTGCGCGAGAGCCACGTCACACTGG	1080
Db	1061	ACTGCGTGTGCCCCCTGAGCTGGTTTGGCCCCCTGGGTGCGCGAGAGCCACGTCACACTGG	1120
Qy	1081	CCAGCCCTGAGGAGACGCGCTGCCACTTCCCGCCCCAAGAACGCTGGCCGGCTGCTCCTGG	1140
Db	1121	CCAGCCCTGAGGAGACGCGCTGCCACTTCCCGCCCCAAGAACGCTGGCCGGCTGCTCCTGG	1180
Qy	1141	AGCTTGACTACGCCGACTTTGGCTGCCCAGCCACCACCACAGCCACAGTGCCACCA	1200
Db	1181	AGCTTGACTACGCCGACTTTGGCTGCCCAGCCACCACCACAGCCACAGTGCCACCA	1240
Qy	1201	CGAGGCCCGTGGTGCGGGAGCCCCACAGCCTTGTCTTCTAGCTTGGCTCCTACCTGGCTTA	1260
Db	1241	CGAGGCCCGTGGTGCGGGAGCCCCACAGCCTTGTCTTCTAGCTTGGCTCCTACCTGGCTTA	1300
Qy	1261	GCCCCACAGCGCCGGCCACTGAGGCCCCCAGCCCGCCCTCCACTGCCCCACCGACTGTAG	1320
Db	1301	GCCCCACAGCGCCGGCCACTGAGGCCCCCAGCCCGCCCTCCACTGCCCCACCGACTGTAG	1360

Qy	1321	GGCCTGTCCCCCAGCCCCAGGACTGCCACCGTCCACCTGCCTCAATGGGGGCACATGCC	1380
Db	1361	GGCCTGTCCCCCAGCCCCAGGACTGCCACCGTCCACCTGCCTCAATGGGGGCACATGCC	1420
Qy	1381	ACCTGGGGACACGGCACCACCTGGCGTGCTTGTGCCCCGAAGGCTTCACGGGCCTGTACT	1440
Db	1421	ACCTGGGGACACGGCACCACCTGGCGTGCTTGTGCCCCGAAGGCTTCACGGGCCTGTACT	1480
Qy	1441	GTGAGAGCCAGATGGGGCAGGGGACACGGCCCAGCCCTACACCAGTCACGCCGAGGCCAC	1500
Db	1481	GTGAGAGCCAGATGGGGCAGGGGACACGGCCCAGCCCTACACCAGTCACGCCGAGGCCAC	1540
Qy	1501	CACGGTCCCTGACCCTGGGCATCGAGCCGGTGAGCCCCACCTCCCTGCGCGTGGGGCTGC	1560
Db	1541	CACGGTCCCTGACCCTGGGCATCGAGCCGGTGAGCCCCACCTCCCTGCGCGTGGGGCTGC	1600
Qy	1561	AGCGCTACCTCCAGGGGAGCTCCGTGCAGCTCAGGAGCCTCCGTCTCACCTATCGCAACC	1620
Db	1601	AGCGCTACCTCCAGGGGAGCTCCGTGCAGCTCAGGAGCCTCCGTCTCACCTATCGCAACC	1660
Qy	1621	TATCGGGCCCTGATAAGCGGCTGGTGACGCTGCGACTGCCTGCCTCGCTCGCTGAGTACA	1680
Db	1661	TATCGGGCCCTGATAAGCGGCTGGTGACGCTGCGACTGCCTGCCTCGCTCGCTGAGTACA	1720
Qy	1681	CGGTCACCCAGCTGCGGGCCCAACGCCACTTACTCCGTCTGTGTCATGCCTTTGGGGCCCCG	1740
Db	1721	CGGTCACCCAGCTGCGGGCCCAACGCCACTTACTCCGTCTGTGTCATGCCTTTGGGGCCCCG	1780
Qy	1741	GGCGGGTGCCGGAGGGCGAGGAGGCCTGCGGGGAGGGCCATACACCCCCAGCCGTCCACT	1800
Db	1781	GGCGGGTGCCGGAGGGCGAGGAGGCCTGCGGGGAGGGCCATACACCCCCAGCCGTCCACT	1840
Qy	1801	CCAACCACGCCCCAGTCACCCAGGCCCCGCGAGGGCAACCTGCCGCTCCTCATTGCGCCCCG	1860
Db	1841	CCAACCACGCCCCAGTCACCCAGGCCCCGCGAGGGCAACCTGCCGCTCCTCATTGCGCCCCG	1900
Qy	1861	CCCTGGCCGCGGTGCTCCTGGCCGCGCTGGCTGCGGTGGGGGCAGCCTACTGTGTGCGGC	1920
Db	1901	CCCTGGCCGCGGTGCTCCTGGCCGCGCTGGCTGCGGTGGGGGCAGCCTACTGTGTGCGGC	1960
Qy	1921	GGGGGCGGGCCATGGCAGCAGCGGCTCAGGACAAAGGGCAGGTGGGGCCAGGGGCTGGGC	1980
Db	1961	GGGGGCGGGCCATGGCAGCAGCGGCTCAGGACAAAGGGCAGGTGGGGCCAGGGGCTGGGC	2020
Qy	1981	CCCTGGAAGTGGAGGGAGTGAAGGTCCCCTTGGAGCCAGGCCCCGAAGGCAACAGAGGGCG	2040
Db	2021	CCCTGGAAGTGGAGGGAGTGAAGGTCCCCTTGGAGCCAGGCCCCGAAGGCAACAGAGGGCG	2080
Qy	2041	GTGGAGAGGCCCTGCCCAGCGGGTCTGAGTGTGAGGTGCCACTCATGGGCTTCCCAGGGC	2100
Db	2081	GTGGAGAGGCCCTGCCCAGCGGGTCTGAGTGTGAGGTGCCACTCATGGGCTTCCCAGGGC	2140
Qy	2101	CTGGCCTCCAGTCACCCCTCCACGCAAAGCCCTACATCTAAGCCAGAGAGAGACAGGGCA	2160
Db	2141	CTGGCCTCCAGTCACCCCTCCACGCAAAGCCCTACATCTAAGCCAGAGAGAGACAGGGCA	2200
Qy	2161	GCTGGGGCCGGGCTCTCAGCCAGTGAGATGGCCAGCCCCCTCCTGCTGCCACACCACGTA	2220

Db	2201		GCTGGGGCCGGGCTCTCAGCCAGTGAGATGGCCAGCCCCCTCCTGCTGCCACACCACGTA	2260
Qy	2221		AGTTCTCAGTCCCAACCTCGGGGATGTGTGCAGACAGGGCTGTGTGACCACAGCTGGGGC	2280
Db	2261		AGTTCTCAGTCCCAACCTCGGGGATGTGTGCAGACAGGGCTGTGTGACCACAGCTGGGGC	2320
Qy	2281		CTGTTCCCTCTGGACCTCGGTCTCCTCATCTGTGAGATGCTGTGGCCCAGCTGACGAGCC	2340
Db	2321		CTGTTCCCTCTGGACCTCGGTCTCCTCATCTGTGAGATGCTGTGGCCCAGCTGACGAGCC	2380
Qy	2341		CTAACGTCCCCAGAACCGAGTGCCTATGAGGACAGTGTCCGCCCTGCCCTCCGCAACGTG	2400
Db	2381		CTAACGTCCCCAGAACCGAGTGCCTATGAGGACAGTGTCCGCCCTGCCCTCCGCAACGTG	2440
Qy	2401		CAGTCCCTGGGCACGGCGGGCCCTGCCATGTGCTGGTAACGCATGCCTGGGGTCTGCTGG	2460
Db	2441		CAGTCCCTGGGCACGGCGGGCCCTGCCATGTGCTGGTAACGCATGCCTGGGGTCTGCTGG	2500
Qy	2461		GCTCTCCCACTCCAGGCGGACCTGGGGGCCAGTGAAGGAAGCTCCCGGAAAGAGCAGAG	2520
Db	2501		GCTCTCCCACTCCAGGCGGACCTGGGGGCCAGTGAAGGAAGCTCCCGGAAAGAGCAGAG	2560
Qy	2521		GGAGAGCGGGTAGGCGGCTGTGTGACTCTAGTCTTGGCCCCAGGAAGCGAAGGAACAAAA	2580
Db	2561		GGAGAGCGGGTAGGCGGCTGTGTGACTCTAGTCTTGGCCCCAGGAAGCGAAGGAACAAAA	2620
Qy	2581		GAAACTGGAAAGGAAGATGCTTTAGGAACATGTTTTGCTTTTTTAAA--ATATATATATT	2638
Db	2621		GAAACTGGAAAGGAAGATGCTTTAGGAACATGTTTTGCTTTTTTAAAATATATATATATT	2680
Qy	2639		TATAAGAGATCCTTTCCCATTTATTCTGGGAAGATGTTTTTCAAACCTCAGAGACAAGGAC	2698
Db	2681		TATAAGAGATCCTTTCCCATTTATTCTGGGAAGATGTTTTTCAAACCTCAGAGACAAGGAC	2740
Qy	2699		TTTGGTTTTTGTAAAGACAAACGATGATATGAAGGCCTTTTGTAAAGAAAAATAAAAGATG	2758
Db	2741		TTTGGTTTTTGTAAAGACAAACGATGATATGAAGGCCTTTTGTAAAGAAAAATAAAAGATG	2800
Qy	2759		AAGTGTGAAA	2768
Db	2801		AAGTGTGAAA	2810